PRESENTATION TYPE: Workshop (165 minutes)
SECONDARY PRESENTATION TYPE: Symposium
IAT/ITS Designation: To Be Determined

TITLE:
Molecular-Based Points of Departure as the New Basis for Chemical Risk Assessment: Are We Ready?

SESSION DESCRIPTION:

Large-scale molecular data, including transcriptomics and high-content imaging, have been available to scientists for over 25 years but have yet to be integrated into regulatory toxicology beyond providing supportive evidence of health effects, such as mode of action analysis for relatively data-rich chemicals. Considering that the vast majority of chemicals in commerce or the environment are data-poor, there are considerable opportunities to leverage molecular data in a more integral way, such as informing dose-response assessment and identifying points of departure (PODs) for use in human health and ecological risk assessment. In a traditional risk assessment, a POD is typically obtained from resource- and animal-intensive low-throughput studies examining apical endpoints (e.g., histopathology, organ weights). More recent efforts have been aimed at increasing throughput of chemical evaluation by integrating PODs derived from molecular-based dose- or concentration-responses obtained using in vitro models or in vivo studies of shorter exposure duration. The aim of this workshop is to present and discuss recent examples that demonstrate how molecular-derived PODs can be used in the chemical sector for risk assessment applications. This workshop will specifically review current regulatory needs, present timely case studies from industry, Health Canada, U.S. EPA, National Toxicology Program, and the University of Ottawa and open the floor to discuss specific paths forward to effectively integrate molecular-derived PODs into the risk assessment process with increased confidence. The first presentation will set the stage for workshop participants by describing the current state of regulatory toxicity assessments and data requirements in the industrial chemical and pesticide spaces. The second speaker will dive deeper into the methods used in deriving molecular-based PODs from transcriptomic data, and the dose-response and temporal concordance of such PODs to traditional apical effect-based PODs. The third speaker will describe the current status of U.S. EPA's high-throughput in vitro modeling effort aimed at analyzing both transcriptome and imaging data to screen and prioritize industrial chemicals as part of a tiered testing framework for hazard characterization. The fourth presentation will review use case studies that illustrate how molecular-derived PODs from short-term exposures in rodents are being used in risk assessment with a focus on comparing pathway-specific to pathway-agnostic PODs and describe relationships between *in vitro* and *in vivo* molecular PODs. The last speaker will provide perspective on fit-for-purpose application of molecular-based data to human health risk assessment, with a focus on deploying molecular PODs in the regulatory toxicology space and describe current use and "on the horizon" uses. Following the presentations, workshop chairs and speakers will engage audience participants in a question and answer session. The goal of this discussion is to be provocative about both the limitations of a molecular POD (e.g., may not easily identify specific hazards) and the opportunities of a molecular POD to dramatically increase chemical toxicity testing throughput while informing safe human use of chemicals.

ENDORSER 1: Risk Assessment Specialty Section
ENDORSER 2: Regulatory and Safety Evaluation Specialty Section
ENDORSER 3: Molecular and Systems Biology Specialty Section

Session Role Order: 1
Session Role: Chair
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SOT Member: Yes
Funding: No SOT Funding
Presentation Title: Chair

Session Role Order: 2
Session Role: Co-Chair
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SOT Member: Yes
Funding: No SOT Funding
Presentation Title: Co-chair

Session Role Order: 3
Session Role: Presenter
Name: Tara Barton-Maclaren
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SOT Member: No
Funding: Yes, funding is being requested for Dr. Barton-Maclaren
Presentation Length: 20 minutes
Presentation Title: Advancing the Use of Molecular-Based Points of Departure to Address Multisectoral Needs for Priority Setting and Chemical Risk Assessment
Presentation Description: Globally there continues to be a rapid evolution in the development of New Approach Methodologies (NAM) with the aim of expediting the rate at which chemicals can be tested through the use of alternative strategies while ensuring that the data quality and relevance is maintained to protect against potential hazards to human health and the environment. In parallel with growing pressure to reduce and eliminate animal testing and the increasing complexity of the chemical landscape, chemicals management faces aggressive assessment mandates and the need to address chemicals with a paucity of toxicological data. Collectively, international governments, industry and academia recognize the imminent promise for emerging technologies to rapidly and effectively support a risk assessment paradigm shift, one of which is through the application of molecular-based points of departure (POD). This presentation will set the stage for the session providing an overview of regulatory requirements for risk assessment and prioritization needs related to industrial chemicals and pesticides illustrating opportunities for context dependent application of NAM. The multisectoral collaboration progressing under the Health and Environmental Sciences Institute (HESI) aimed at identifying and

addressing the scientific uncertainties associated with the use of a transcriptomic POD in risk assessment will be highlighted and current challenges for the use of molecular-based PODs for decision-making introduced.

Session Role Order: 4
Session Role: Presenter
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Funding: No SOT Funding
Presentation Length: 20 minutes
Presentation Title: Transcriptome Points of Departure: Derivation Methodology, In Vivo Stability, and Concordance to In Vivo Short-Term Apical Points of Departure
Presentation Description: This presentation will describe methods to generate transcriptome points of departure and examine their temporal stability and concordance to short-term study apical POD values. Developing a consensus method to derive a molecular POD will be crucial to use the methodology within a regulatory framework; however, no consensus exists currently. Two methods to derive a transcriptional POD will be presented. The first method is based upon the historical practice of deriving a gene set-based (e.g. Gene Ontology terms) POD using the Functional Classification step with BMDExpress software. The second method to be presented will explore removing the Functional Classification step and instead utilizing POD values at the level of individual genes. Both of these methods are agnostic to mechanism in that a direct linkage between the gene set or individual genes driving the POD and the apical outcome is not obtained. In effect, the transcriptional POD may represent the first point along the dose response curve of "concerted molecular change". Using rat liver TG-GATES transcriptome data across 79 molecules and eight time points, the stability of the transcriptome POD over various durations of exposure will be presented. Finally, concordance of the rat liver transcriptional POD to a short-term (29 day) rat "systemic" apical POD will be shown using data across 79 TG-GATES molecules. This presentation will highlight the conclusion that a rat transcriptional POD agnostic to mechanism or mode-of-action is 1) robust to exposure duration and 2) predictive of an in vivo apical POD. This information will set the stage for the subsequent presentations exploring additional in vitro and in vivo case studies comparing the predictivity of a transcriptional (or high content imaging-based) POD for an apical POD and outlining the potential use of molecular PODs in regulatory contexts.

Session Role Order: 5
Session Role: Presenter
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SOT Member: Yes
Funding: No SOT Funding
Presentation Length: 20 minutes
Presentation Title: In Vitro Molecular PODs from High-Throughput Profiling Assays
Presentation Description: US EPA has been exploring the use of New Approach Methodologies (NAMs) for hazard characterization of environmental chemicals for more than a decade. In order to increase screening efficiency and coverage of human biological space in the context of *in vitro* hazard characterization, the recently released Blueprint for Computational Toxicology at US EPA advocates the use of high-throughput profiling (HTP) assays as the first step in a NAMs-based tiered testing framework for hazard characterization. Ideally, HTP assays should be capable of being deployed in high-throughput screening format across multiple human-derived *in vitro* models and provide high content data that can be used to assess perturbation of intact biological networks and/or cellular functions and inform putative mechanism-of-action prediction. To date, US EPA has identified two assays that satisfy these criteria: 1) high-throughput transcriptomics (HTTr) using TempO-Seq and 2) high-throughput phenotypic profiling (HTPP) using Cell Painting. Information gleaned from these HTP assays include molecular point-of-departures (PODs) based on threshold concentrations for perturbation of cellular biology. These molecular PODs may either be agnostic to chemical mechanism or anchored to established key events or mechanisms-of-action based on prior knowledge or inference from the observed changes in gene expression or cellular morphology. A brief overview of each technology will be presented along with demonstration of how data from each of these assays can be used to generate molecular PODs through the use of high-throughput concentration response modeling and conversion to administered equivalent doses (AEDs) using high-throughput toxicokinetic modeling and reverse dosimetry. Molecular PODs derived from the HTP assays will be compared across technologies and across cell lines as well as to molecular PODs that can be derived from "traditional" HTS assays within the ToxCast / Tox21 assay suite. Lastly, the utility of the molecular PODs for chemical safety assessment will be demonstrated in a screening for prioritization context using bioactivity:exposure ratio (BER) analysis. Participants in the session will gain a broader understanding of emerging high-throughput technologies and their potential applications for NAMs-based chemical safety assessment. *This abstract does not reflect USEPA policy.*

Session Role Order: 6
Session Role: Presenter
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SOT Member: Yes
Funding: Yes, funding is being requested for Carole Yauk.
Presentation Length: 20 minutes
Presentation Title: Case Studies on the Use of Transcriptomic Points of Departure
Presentation Description: Case studies provide important opportunities for the regulatory and research communities to work together to define context of use and advance new approach methodologies. Benchmark-dose modeling of transcriptomic data has numerous potential applications in regulatory decision making, from tiered testing/prioritization to derivation of a molecular-based point of departure (mPOD) for use in risk assessment. Exemplary case studies on different applications and approaches will be presented. Perspectives will be given on lessons learned from case studies on the flame retardant hexabromocyclododecane in which a tiered testing approach was employed and a set of perflourinated

chemicals in which transcriptomics was used to characterize relative potency and derive bioactivity exposure ratios. A point of emphasis will be placed on illustrating the impact that the use of the in vitro and in vivo transcriptomic approaches has on determining a mPOD and how these compare to PODs based on guideline toxicological assessment data (i.e., a pathology based POD). These case studies will provide a tangible context for understanding the applicability of mPODs and the implications for using them for risk assessment.

Session Role Order: 7
Session Role: Presenter
Name: Jason Lambert
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SOT Member: Yes
Funding: No SOT Funding
Presentation Length: 20 minutes
Presentation Title: Quantitative Integration of NAMs into Regulatory Decision-Making: Current State of the Science and a Michaelis-Menten-based Acceptance Path Forward
Presentation Description: The vast majority of chemicals found in commerce and the environment are data-poor chemicals, and as such are commonly unaccounted for in formal quantitative evaluations of health risks to human populations. This is due to the lack of available points-of-departure (POD) for use in derivation of non-cancer or cancer values. New Approach Methodologies (NAM), such as structure-activity/read-across, transcriptomics, in vitro cell bioactivity, high-throughput toxicokinetics, and several other NAM platforms and approaches present a significant opportunity to expedite the assessment of chemicals both qualitatively and quantitatively. Leveraging NAM data that can readily provide structural, physicochemical, and biological information associated with pathways and processes respondent to exposure to parent chemicals and/or their metabolite(s) may facilitate hazard identification ranging from data-gap filling to pathway-based inferences for organ or tissue-based toxicity. As discussed throughout this workshop, several NAMs provide a rapid mechanism in which in vivo dose and/or in vitro concentration-response data can be used to generate PODs for potential risk assessment applications, from basic screening and prioritization, up to NAM-based human health risk assessment. This presentation will provide current state of the science examples of the application of NAM-based PODs in regulatory chemical decision-making in the U.S. EPA, and it will set-the-stage for discussions surrounding this timely issue. *This abstract does not reflect U.S. EPA policy.*